(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 February 2006 (16.02.2006)

PCT

(10) International Publication Number
WO 2006/016174 A1

(51) International Patent Classification[7]: C07D 277/40, 277/46, 417/12, A61K 31/424, 31/427, A61P 3/10

(21) International Application Number: PCT/GB2005/003170

(22) International Filing Date: 12 August 2005 (12.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0418058.4 12 August 2004 (12.08.2004) GB

(71) Applicant (*for all designated States except US*): **PROSIDION LIMITED** [GB/GB]; Watlington Road, Oxford, Oxfordshire OX4 6LT (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **FYFE, Matthew, Colin, Thor** [GB/GB]; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB). **NAUD, Frederic** [FR/CH]; Solvias AG, WRO-1055.6.16, Mattenstrasse 22, CH-4002 Basel (CH).

(74) Agent: **BLAKEY, Alison**; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB).

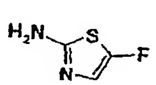
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FLUORINATION PROCESS OF PROTECTED AMINOTHIAZOLE



(I)

(57) Abstract: A process for the production of fluorinated compound formula (I) comprising fluorination of a protected aminothiazole. Compounds formula (I) are useful in the preparation of activators of glucokinase.

WO 2006/016174 A1

FLUORINATION PROCESS OF PROTECTED AMINOTHIAZOLE

BACKGROUND OF THE INVENTION

The present invention is directed to a process for the production of fluorinated compounds. In particular, the invention is directed to a process for the production of a fluorinated compound of use in the production of pharmaceutically active compounds, especially compounds which are useful as activators of glucokinase for the treatment of type II diabetes.

International Patent Applications PCT/US04/03968 and PCT/GB2005/050053 (published after the priority date of the present application) disclose various tri(cyclo) substituted amide compounds which are modulators of glucokinase and are useful in the prophylactic or therapeutic treatment of hyperglycemia and type II diabetes. Certain of these compounds, for example (2*R*)-2-(4-cyclobutanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide, (2*R*)-2-(4-cyclopropanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide and 2(*R*)-2-(4-cyclopropanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-((*R*)-3-oxocyclopentyl)propionamide, contain a 5-fluorothiazole group. There is a need for efficient processes for the production of 2-amino-5-fluorothiazole and acid addition salts thereof, e.g. the hydrochloride salt, which are useful as intermediates for the synthesis of the therapeutic compounds.

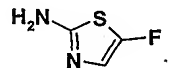
2-Amino-5-fluorothiazole is disclosed by name in US4094785, US4086240, DE2724614 and US4046768, however no methods for the synthesis of this compound are disclosed. The production of 2-amino-5-fluorothiazole trifluoroacetate by addition of trifluoroacetic acid to a solution of (5-fluorothiazol-2-yl)carbamic acid tert-butyl ester is described in WO2004/063179 but no details for the preparation of the carbamic acid ester starting material or characterization of the product are provided. PCT/US04/03968 describes the synthesis of 2-amino-5-fluorothiazole hydrochloride from 5-bromothiazol-2-ylamine hydrobromide via *N*-(5-bromothiazol-2-yl)-2,2,2-trifluoroacetamide. However, this process is not particularly efficient for the synthesis of such compounds on a commercial scale. Therefore, there is a need for further efficient processes for the production of 2-amino-5-fluorothiazole.

SUMMARY OF THE INVENTION

A process for the production of 2-amino-5-fluorothiazole or an acid addition salt thereof.

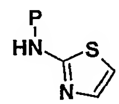
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the production of a compound of formula (I):



(I)

or an acid addition salt thereof, comprising fluorination of a compound of formula (II):



(II)

wherein P is a protecting group, followed by removal of the protecting group and optional salt formation.

Protecting groups that P may represent include any amino protecting groups such as those described in Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition. Particular protecting groups which may be mentioned include acetyl, pivaloyl and tert-butoxycarbonyl (Boc), a preferred protecting group is tert-butoxycarbonyl.

In a first and preferred embodiment of the invention the fluorination reagent used in the method is an electrophilic fluorinating agent e.g. comprising an active N-fluorine bond. Examples of electrophilic fluorinating agents include N-fluorosulfonamides and N-fluorosulfonimides as described for example in A. J. Poss et al., Speciality Chemicals Magazine, April 2003, 36-40 and E. C. Taylor et al., Org. Prep. Proceed. Int., 1997, 29, 221-223. Preferred fluorinating reagents are N-fluorosulfonimides, a particularly preferred fluorinating agent is N-fluorobenzenesulfonimide.

The fluorination is preferably conducted at reduced temperature, for example a temperature of about -50°C.

The dianion of the compound of formula (II) is preferably prepared prior to addition of the fluorination reagent by deprotonation with an appropriate base e.g. an organolithium or organomagnesium reagent e.g. a Grignard reagent. Preferred bases are organolithium reagents e.g. n-, tert-, or sec-butyl lithium, methyl lithium and phenyl lithium, a particularly preferred base is tert-butyl lithium. Preferably at least 2 equivalents, especially about 2 equivalents e.g. 2.2 equivalents, of the base relative to the compound of formula (II) are used.

The dianion of the compound of formula (II) is stable for several hours at a temperature of e.g. from about -50 to 0°C.

In this preferred embodiment the fluorination reaction is preferably conducted in a suitable solvent, preferably a non-polar aprotic solvent such as ether, tetrahydrofuran or dioxane, preferably tetrahydrofuran.

In a second embodiment the reagent is an electrophilic aromatic substitution reagent such as 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®), see G. S. Lal, J. Org. Chem., 1993, 58, 2791-2796.

In this second embodiment the fluorination reaction is preferably conducted in a suitable solvent, for example acetonitrile.

In this second embodiment the fluorination reaction is preferably conducted at an elevated temperature, for example the reflux temperature of the solvent.

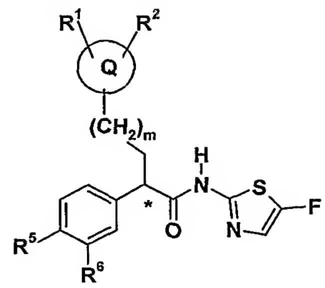
Prior to removal of the protecting group the fluorinated intermediate produced from the compound of formula (I) according to the method of the invention may be further purified by recrystallisation. A suitable recrystallisation solvent is a mixture of trifluoroethanol and formic acid, e.g. at a ratio of about 100:1 v/v.

Suitable acid addition salts of 2-amino-5-fluorothiazole include those formed with inorganic and organic acids. Such acids include, for example, acetic, trifluoroacetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, hydrofluoric isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, triflic acid and the like. Particularly preferred are the hydrohalide salts especially the hydrochloride.

Acid addition salts of 2-amino-5-fluorothiazole may be prepared by reaction of the amine with the appropriate acid. The hydrochloride salt is preferably prepared by dissolving the amine in a suitable solvent e.g. tetrahydrofuran or dioxane, preferably dioxane, and bubbling through HCl gas. The resulting hydrochloride salt may be isolated by the addition of a cosolvent, e.g. diethylether, and filtration of the resulting solid.

The compounds of formula (II) may be prepared from 2-aminothiazole by methods known to those skilled in the art, for example as described by C. Poupat, Tetrahedron, 58, 2002, 4201-4215.

The invention also provides the use of the compounds of formula (I) prepared as described above as an intermediate for the manufacture of a compound of formula (III), or a pharmaceutically acceptable salt thereof:



(III)

wherein Q is an aryl, a 5- or 6-membered heteroaryl, or a 4–8-membered heterocyclic ring;

R^1 and R^2 each independently are hydrogen, hydroxy, halogen, cyano, nitro, vinyl, ethynyl, methoxy, OCF_nH_{3-n}, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, CHO, or C_{1-2}alkyl optionally substituted with 1-5 independent halogen, hydroxy, cyano, methoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, or SO_2CH_3 substituents; or R^1 and R^2 together form a carbocyclic or heterocyclic ring; or R^1 and R^2 may be taken together to represent an oxygen atom attached to the ring via a double bond;

R^5 and R^6 each independently are hydrogen, hydroxy, halogen, cyano, nitro, CO_2R^7, CHO, COR^8, $C(OH)R^7R^8$, $C(=NOR^7)R^8$, $CONR^9R^{10}$, SR^7, SOR^8, SO_2R^8, $SO_2NR^9R^{10}$, $CH_2NR^9R^{10}$, NR^9R^{10}, $N(C_{0-4}alkyl)SO_2R^8$, $NHCOR^7$, or a C_{1-4}alkyl group, C_{2-4}alkenyl group, C_{2-4}alkynyl group, C_{1-4}alkoxy group, aryl group, or heteroaryl group, wherein any group optionally is substituted with 1-6 independent halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, CF_nH_{3-n}, aryl, heteroaryl, $-COC_{1-2}alkyl$, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, SCH_3, $SOCH_3$, SO_2CH_3, or $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$ substituents; or R^5 and R^6 together form a 5–8-membered carbocyclic or heterocyclic ring;

R^7 is hydrogen, or a C_{1-4}alkyl group, C_{2-4}alkenyl group, C_{2-4}alkynyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4–7-membered heterocyclic group, wherein any group optionally is substituted with 1-6 independent halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, C_{3-7}cycloalkyl, 4–7-membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, CO_2H, $-COC_{1-2}alkyl$, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, or $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$ substituents;

R^8 is a C_{1-4}alkyl group, C_{2-4}alkenyl group, C_{2-4}alkynyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4–7-membered heterocyclic group, wherein any group optionally is substituted with 1-6 independent halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, C_{3-7}cycloalkyl, 4–7-membered heterocyclic ring, CF_nH_{3-n},

aryl, heteroaryl, CO_2H, COC_{1-2}alkyl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, or $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$ substituents;

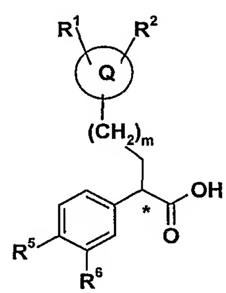
R^9 and R^{10} each independently are hydrogen, or a C_{1-4}alkyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4–7-membered heterocyclic group, wherein any group optionally is substituted with 1-6 independent halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, C_{3-7}cycloalkyl, 4–7-membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, COC_{1-2}alkyl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, or $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$ substituents; or R^9 and R^{10} together form a 6–8-membered heterobicyclic ring system or a 4–8-membered heterocyclic ring which optionally is substituted with 1–2 independent C_{1-2}alkyl, CH_2OCH_3, COC_{0-2}alkyl, hydroxy, or SO_2CH_3 substituents;

n is 1, 2 or 3; and

m is 0 or 1.

In the compounds of formula (III) the carbon atom linking the aryl ring and Q-bearing sidechain to the carbonyl carbon is a chiral centre. Accordingly, the compound may be present either as a racemate, or as a single enantiomer in the (*R*)- or (*S*)-configuration. The (*R*)-enantiomers are preferred.

The compounds of formula (III) may be prepared by the condensation of the amine of formula (I) or a salt thereof, with a carboxylic acid of formula (IV):

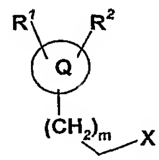


(IV)

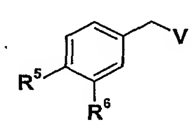
wherein R^1, R^2, R^5, R^6, Q and m are as defined for formula (III), using a variety of coupling conditions, e.g. polymer supported carbodiimide-1-hydroxybenzotriazole in *N,N*-dimethylformamide at 20°C (for representative procedures, see http://www.argotech.com/PDF/resins/ps_carbodiimide.pdf and available from Argonaut Technologies, Inc., Foster City, California). Preferably the condensation is performed employing a reagent that minimises racemisation of the chiral centre, e.g. benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (J. Coste et al. *Tetrahedron Lett.* 1990, *31*, 205–208), to furnish enantiopure (*R*)-amides of Formula (III).

Alternatively the coupling reaction may employ an activated derivative of the carboxylic acid of formula (IV), for example a protected ester or acid chloride thereof which may be prepared by methods known to those skilled in the art, in which case the coupling may be conducted in the presence of collidine or another suitable pyridine derivative.

The carboxylic acids of formula (IV) may be prepared by reaction of a compound of formula (V) with a compound of formula (VI):



(V)



(VI)

wherein R^1, R^2, R^5, R^6, Q and m are as defined above, V is CO_2R^{11} or CO_2CH_2Ph, and X is chloro, bromo, iodo, or $-OSO_2R^{12}$; wherein R^{11} is C_{0-4}alkyl and R^{12} is C_{1-4}alkyl, optionally substituted with one or more fluorines, or optionally substituted aryl.

The halides and sulfonate esters (V) are commercially available or are readily prepared using known techniques. These alkylating agents may be reacted with the dianions of the phenylacetic acids (VI), generated at –78°C in tetrahydrofuran with ≥2 equivalents of a strong base, such as lithium diisopropylamide, to generate (IV) directly (F. T. Bizzarro et al., WO 00/58293). Alternatively, the α-carbanion of phenylacetic ester (VI), generated at –78°C in tetrahydrofuran by a strong base, such as lithium bis(trimethylsilyl)amide (L. Snyder et al., J. Org. Chem. 1994, *59*, 7033–7037), can be alkylated by (V) to give α-substituted esters. Saponification of these esters, employing, for example, sodium hydroxide in aqueous methanol at 20°C to reflux, leads to the carboxylic acids (IV).

The carboxylic acids of formula (IV) may alternatively be synthesized by enantioselective hydrogenation of the corresponding (*E*)-2-(4-cycloalkanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid as described in the Examples.

Preferred compounds of formula (III) prepared according to this aspect of the invention include those compounds in which:

Q is preferably 2-furyl, 2-thienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyranyl, or 1,1-dioxo-tetrahydrothiopyranyl; more preferably 4-tetrahydropyranyl or 4-tetrahydrothiopyranyl; most preferably 4-tetrahydropyranyl.

When Q is a heteroaryl or heterocyclic group it is preferably linked to the $-(CH_2)_m-$ group through a carbon atom.

When Q is a heteroaryl group it preferably does not have a substituent R^1 or R^2 other than hydrogen at a position adjacent to point of attachment to the $-(CH_2)_m-$ group.

R^1 and R^2 are preferably hydrogen.

R^5 and R^6 are preferably not both hydrogen.

R^5 is preferably CF_3, SOR^8, SO_2R^8, $SO_2NR^9R^{10}$, $NHSO_2R^8$, or triazolyl; more preferably SOR^8, SO_2R^8, or $SO_2NR^9R^{10}$; most preferably SO_2R^8 or $SO_2NR^9R^{10}$, especially SO_2R^8. In particular R^5 is SO_2C_{3-4}cycloalkyl, especially SO_2cyclopropyl.

R^6 is preferably hydrogen, chloro, fluoro, or trifluoromethyl; more preferably hydrogen.

R^7 and R^8 are preferably C_{1-4}alkyl, C_{3-7}cycloalkyl, heteroaryl, or 4–7-membered heterocyclic group; more preferably C_{1-3}alkyl, 4–6-membered heterocyclic group, or C_{3-5}cycloalkyl; most preferably methyl, ethyl, *n*-propyl, cyclopropyl, cyclobutyl, oxetanyl, or tetrahydrofuryl, and especially methyl, ethyl, *n*-propyl, cyclopropyl, or cyclobutyl, especially cyclopropyl.

When R^5 and/or R^6 are CO_2R^7 or SR^7, R^7 is preferably not hydrogen.

R^9 and R^{10} are preferably independently C_{0-4}alkyl e.g. one of R^9 and R^{10} is hydrogen and the other is ethyl, or combine to form a 4–8-membered heterocyclic ring. R^9 and R^{10} are preferably not both hydrogen.

m is preferably 0.

n is preferably 2 or 3.

A preferred group of compounds are compounds of Formula (III), or pharmaceutically acceptable salts thereof, wherein:

Q is 4-tetrahydropyranyl;

R^1 and R^2 are hydrogen;

R^5 is SO_2R^8, or $SO_2NR^9R^{10}$;

R^6 is hydrogen;

R^8 is a C_{3-5}cycloalkyl group or a 4–6-membered heterocyclic group, and, in addition;

R^9 and R^{10} are independently C_{0-4}alkyl, provided that R^9 and R^{10} are not both hydrogen; and

m is 0.

A more preferred group of compounds are compounds of Formula (III), or pharmaceutically acceptable salts thereof, wherein:

Q is 4-tetrahydropyranyl;

R^1 and R^2 are hydrogen;

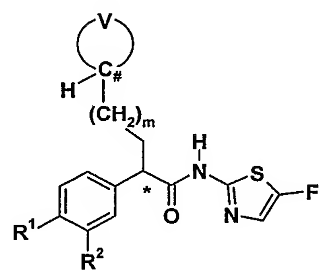
R^5 is SO_2R^8;

R^6 is hydrogen;

R^8 is a C_{3-5}cycloalkyl group; and

m is 0.

The invention also provides the use of the compounds of formula (I) prepared as described above as an intermediate for the manufacture of a compound of formula (VII), or a pharmaceutically acceptable salt thereof:



(VII)

wherein V is $(CH_2)_k$ where one CH_2 group may optionally be replaced by CH(OH), C=O, C=NOH, C=NOCH$_3$, CHX, CXX^1, CH(OCH$_3$), CH(OCOCH$_3$), CH(C_{1-4}alkyl), or C(OH)(C_{1-4}alkyl);

X and X^1 are independently selected from fluoro and chloro;

R^1 and R^2 are independently selected from hydrogen, halogen, hydroxy, amino, cyano, nitro, SR^3, SOR^3, SO_2R^3, $SO_2NR^4R^5$, $NHSO_2R^3$, or a C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, or heteroaryl group, wherein any group is optionally substituted with 1 to 5 substituents independently selected from halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, –N(C_{0-2}alkyl)(C_{0-2}alkyl), C_{1-2}alkyl, CF_nH_{3-n}, aryl, heteroaryl, –CON(C_{0-2}alkyl)(C_{0-2}alkyl), SCH_3, $SOCH_3$, SO_2CH_3, and –SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl);

R^3 is a C_{1-4}alkyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4- to 7-membered heterocyclic group, wherein any group is optionally substituted with 1 to 5 substituents independently selected from halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, –N(C_{0-2}alkyl)(C_{0-2}alkyl), C_{1-2}alkyl, C_{3-7}cycloalkyl, 4- to 7-membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, COC$_{1-2}$alkyl, –CON(C_{0-2}alkyl)(C_{0-2}alkyl), $SOCH_3$, SO_2CH_3, and –SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl);

R^4 and R^5 are independently hydrogen, or a C_{1-4}alkyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4- to 7-membered heterocyclic group, wherein any group is optionally substituted with 1 to 5 substituents independently selected from halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, –N(C_{0-2}alkyl)(C_{0-2}alkyl), C_{1-2}alkyl, C_{3-7}cycloalkyl, 4- to 7-

membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, and $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$;

or R^4 and R^5 together form a 4- to 8-membered heterocyclic ring which is optionally substituted with 1 or 2 substituents independently selected from C_{1-2}alkyl and hydroxy;

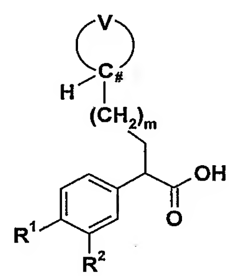
k is an integer from 2 to 7;

m is 0 or 1; and

n is 1, 2 or 3.

In the compounds of formula (VII) the carbon atom linking the aryl ring and the -HC<>V-bearing sidechain to the carbonyl carbon is a chiral centre. Accordingly, the compound may be present either as a racemate, or as a single enantiomer in the (*R*)- or (*S*)-configuration. The (*R*)-enantiomers are preferred.

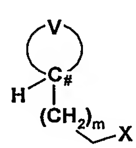
The compounds of formula (VII) may be prepared by the condensation of the amine of formula (I) or a salt thereof, with a carboxylic acid of formula (VIII) or an activated derivative thereof:



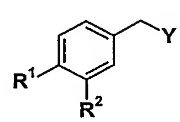
(VIII)

wherein V, R^1, R^2 and m are as defined for formula (VII) using a variety of coupling conditions as described above for the synthesis of the compounds of formula (III).

The carboxylic acids of formula (VIII) may be prepared by reaction of a compound of formula (IX) with a compound of formula (X):



(IX)



(X)

wherein V, R^1, R^2 and m are as described above, Y is CO_2R^{12} wherein R^{12} is hydrogen, C_{1-4}alkyl or benzyl; and X is chloro, bromo, iodo, or $-OSO_2R^{13}$, wherein R^{13} is C_{1-4}alkyl, optionally substituted with one or more fluorines, or optionally substituted aryl.

The halides and sulfonate esters (IX) and the phenylacetic acids and esters (X) are commercially available or are readily prepared using known techniques, for example as

described in International Patent Publication Nos. WO2000/058293, WO2001/044216 and WO2003/095438. These alkylating agents may be reacted with the dianions of the phenylacetic acids (X), generated at –78°C in tetrahydrofuran with ≥2 equivalents of a strong base, such as lithium diisopropylamide, to generate (VII) directly (F. T. Bizzarro et al., WO2000/58293). Alternatively, the α-carbanion of phenylacetic ester (X), generated at –78°C in tetrahydrofuran by a strong base, such as lithium bis(trimethylsilyl)amide (L. Snyder et al., *J. Org. Chem.* 1994, *59*, 7033–7037), can be alkylated by (IX) to give α-substituted esters. Saponification of these esters, employing, for example, sodium hydroxide in aqueous methanol at 20°C to reflux, leads to the carboxylic acids (VII).

Preferred compounds of formula (VII) prepared according to this aspect of the invention include those compounds in which:

The group formed by –HC< and >V represents oxocycloalkyl or hydroxycycloalkyl, e.g. 3-oxocyclopentyl particularly (R)-3-oxocyclopentyl, 4-oxocyclohexyl or 3-hydroxycyclopentyl, especially (R)-3-oxocyclopentyl.

R^1 and R^2 are not both hydrogen.

R^1 is CF_3, SOR^3, SO_2R^3, $SO_2NR^4R^5$, $NHSO_2R^3$, or triazolyl; more preferably SOR^3, SO_2R^3, or $SO_2NR^4R^5$; most preferably SO_2R^3 or $SO_2NR^4R^5$, especially SO_2R^3. In particular R^1 is SO_2C_{3-4}cycloalkyl, especially SO_2cyclopropyl.

R^2 is hydrogen, chloro, fluoro, or trifluoromethyl; more preferably hydrogen or chloro.

R^3 is C_{1-3}alkyl or C_{3-4}cycloalkyl, more preferably C_{3-4}cycloalkyl, especially cyclopropyl.

R^4 and R^5 are independently hydrogen or C_{1-4}alkyl, e.g. one of R^4 and R^5 is hydrogen and the other is ethyl, or combine to form a 4- to 8-membered heterocyclic ring. R^4 and R^5 are preferably not both hydrogen.

m is 0.

V is $(CH_2)_k$ where one CH_2 group is replaced by CH(OH) or C=O.

k is 4 or 5.

Various functional groups present in the compounds described above and intermediates for use in the preparation thereof may be produced by functional group conversions known to those skilled in the art. For example sulfonyl groups may be produced by oxidation of the corresponding sulfanyl group using e.g. mCPBA.

Further details for the preparation of the compounds are found in the examples.

During the synthesis of the compounds described above, labile functional groups in the intermediate compounds, e.g. hydroxy, oxo, carboxy and amino groups, may be protected.

The protecting groups may be removed at any stage in the synthesis of the compounds. A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

The invention also provides a pharmaceutical composition comprising a compound of formula (III) or (VII), or a pharmaceutically acceptable salt thereof, produced according to the method described above, in combination with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of prophylactic or therapeutic treatment of a condition where activation of glucokinase is desirable comprising a step of administering an effective amount of a compound of formula (III) or (VII), produced according to the method described above, or a pharmaceutically acceptable salt thereof.

The invention also provides a method of prophylactic or therapeutic treatment of hyperglycemia or diabetes, particularly type II diabetes, comprising a step of administering an effective amount of a compound of formula (III) or (VII), produced according to the method described above, or a pharmaceutically acceptable salt thereof. In this aspect of the invention the compound of formula (III) or (VII), may be administered in combination with one or more other anti-hyperglycemic agents or anti-diabetic agents.

The invention also provides a method of prevention of diabetes, particularly type II diabetes, in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering an effective prophylactic amount of a compound of formula (III) or (VII), produced according to the method described above, or a pharmaceutically acceptable salt thereof.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

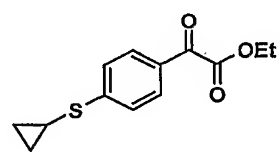
EXAMPLES

Materials and methods:

Column chromatography was carried out on SiO_2 (40–63 mesh). LCMS data were obtained using a Waters Symmetry 3.5µ C_{18} column (2.1 × 30.0mm, flow rate 0.8mL/min) eluting

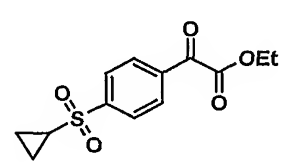
with solvent A (5% MeCN in H_2O) and solvent B (MeCN solution containing 0.1% HCO_2H) over 6min and UV detection at 220nm. Gradient information: 0.0–1.2min: 100% A; 1.2–3.8min: Ramp up to 10% A–90% B; 3.8–4.4min: Hold at 10% A–90% B; 4.4–5.5min: Ramp up to 100% B; 5.5–6.0min: Return to 100% A. The mass spectra were obtained employing an electrospray ionisation source in the positive (ES^+) ion mode. Prep HPLC purification was carried out using a Lunar 10 μ ODS2 (250 x 21.2mm; flow rate 20mL/min) eluting with solvent A (0.05% TFA, 10% MeCN, 90% water) and solvent B (0.05% TFA, 90% MeCN, 10% water) and UV detection at 215 nm. Gradient information: 0.0–0.2 min: 90% A, 10% B; 0.2–10.0 min: Ramp up to 10% A, 90% B; 10.0–15.0 min: 10% A, 90% B; 15.0–16.0 min: Return to 90% A, 10% B.

Preparation 1: Ethyl (4-cyclopropylsulfanylphenyl)oxoacetate



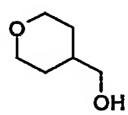
$AlCl_3$ (104.6g, 0.79mol) was suspended in CH_2Cl_2 (1.15L) and cooled in an ice/salt bath to 0°C with stirring. Ethyl chlorooxoacetate (84.8g, 0.62mol) was then added over a period of 10min, during which time the temperature was maintained between 0 and 2°C. The mixture was then stirred for a further 30min at 0°C, before the addition of cyclopropylphenylsulfide (85.0g, 0.57mol) over a period of 45min, during which time the temperature remained between 0 and 8°C. The resulting mixture was allowed to warm to room temperature and stirred for a further 2h. After this time ice/water (275mL) was added, with ice bath cooling maintaining the temperature at 20°C. The organic layer was separated and washed with water (2 x 250mL), saturated $NaHCO_3$ solution (2 x 250mL) and again with water (1 x 250mL). The organic fraction was then dried ($MgSO_4$) filtered and the solvent removed to provide the title compound (134g, 94% yield). NMR was consistent with the above structure.

Preparation 2: Ethyl (4-cyclopropylsulfonylphenyl)oxoacetate



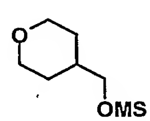
To a stirred solution of Preparation 1 (49.4g, 0.2mol) in CH_2Cl_2 (180mL) was added a solution of m-chloroperoxybenzoic acid (92.0g, 0.40mol, calc as 75% strength) in CH_2Cl_2 (650mL) over 45min with the temperature maintained at 15-25°C. TLC (CH_2Cl_2:ethyl acetate 1:10) showed that starting material still remained. Further m-chloroperoxybenzoic acid (3.4g) in CH_2Cl_2 was added and the reaction stirred for 30min. A second TLC still showed the presence of some starting material, and additional m-chloroperoxybenzoic acid (3.4g) was added and the reaction stirred for a further 2h. TLC showed a small amount of starting material so a final quantity of m-chloroperoxybenzoic acid (1.0g) was added and the reaction continued for 1h. Sodium carbonate solution (2M, 500mL) was then added and the aqueous layer was separated, the pH raised to 9-10 and reextracted with CH_2Cl_2. The organic extracts were combined, washed with water (2 x 400ml), dried ($MgSO_4$), filtered and the solvent removed under vacuum (54.1g, 96% yield). NMR was consistent with the above structure.

Preparation 3: (Tetrahydropyran-4-yl)methanol



To a suspension of $LiAlH_4$ (56g, 1.47mol) in diethyl ether (2L) under argon was added methyl tetrahydro-2H-pyran-4-carboxylate (270g, 1.88mol) in diethyl ether (ca. 200mL) under reflux over a period of 1.75h. After addition was complete reflux was continued for a further 1h. TLC (diethyl ether) indicated a small amount of ester remained, so further $LiAlH_4$ (10g, 0.26mol) was added and reflux continued for 1h. Water (66mL) was added, then 15% NaOH solution (66mL), followed by further water (198mL). The solid was filtered and dried to give the crude product, which was redissolved in DCM (800 ml), dried ($MgSO_4$),filtered and the solvent removed to afford the title compound (207 g, 94% yield). NMR was consistent with the above structure.

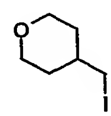
Preparation 4: Methanesulfonicacid (tetrahydropyran-4-yl)methyl ester



To a mixture of Preparation 3 (216.5g, 1.87mol) and triethylamine (299mL) in DCM (1.3L) at <10°C was added under argon a solution of methanesulfonyl chloride (236g, 160mL)

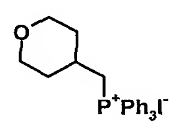
in DCM (200mL) over 2h 50min, maintaining the temperature at 5-10°C throughout. Subsequent washing with water (1L), 1M HCl (500mL), 5% $NaHCO_3$ (300mL), water (300mL), drying ($MgSO_4$) and then removal of the solvent afforded the title compound (328g, 90% yield). NMR was consistent with the above structure.

Preparation 5: 4-Iodomethyltetrahydropyran



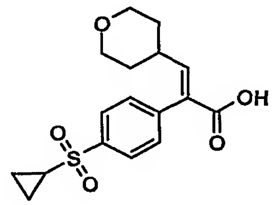
A mixture of Preparation 4 (328g, 1.69mol) and sodium iodide (507g, 3.4mol) in acetone (3.3L) was refluxed for 4h. TLC (diethyl ether) showed significant mesylate remaining so further sodium iodide (127g, 0.65mol) was added and reflux continued for 16h. The mixture was cooled and filtered. The resulting cake was washed with acetone, dried, and then partitioned between diethyl ether (800mL) and water (800mL). The aqueous phase was re-extracted with diethyl ether (200mL), the ether extracts combined and washed with 10% *sodium thiosulphate solution (300mL) which decolourised the extract. Final washing with* water (300mL), drying ($MgSO_4$) and then removal of the solvent provided the title compound (365g, 92% yield). NMR was consistent with the above structure.

Preparation 6: Triphenyl(tetrahydropyran4-ylmethyl)phosphonium iodide



A mixture of Preparation 5 (350g, 1.55M) and triphenylphosphine (406g, 1.55M) in acetonitrile (1.6L) was heated under reflux. After 27h the mixture was cooled and filtered, washed with diethyl ether and dried in air to provide a white solid (504g). Filtrate and washings were returned to reflux and concentrated to 750mL, reflux was maintained for 16h before cooling and dilution with diethyl ether (ca 1.2L). A precipitate formed which was stirred for 30min before being filtered, washed with diethyl ether (2 x 300mL) and dried in air to yield a further crop (100g). Overall yield of the title compound (604 g, 80%). RT = 2.7min; m/z (ES^+) = 361.2.

Preparation 7: (*E*)-2-(4-Cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid



To a suspension of Preparation 6 (2.49kg, 5.10mol) in dry THF (5L) maintained between -5 and 0°C was added a solution of lithium hexamethyldisilazide (1.05M, 4.39kg, 5.18mol) over 30min. The resulting mixture was then warmed to 15°C and stirred for 2h before recooling to between 0 and 5°C. A solution of Preparation 2 (1.25kg, 4.43mol) in THF (2.5L) was then added over 1h, during which time the temperature was maintained between 0 and 5°C, before a period of 16h at between 20 and 25°C. Subsequently, brine (17% w/w, 3.8L) was added and the phases separated with the aid of additional brine (1.3L). The aqueous phase was reextracted with methyl t-butyl ether (2 x 2.5L) and the combined organic extracts washed with brine (2 x 3.8L). The solvents were removed under vacuum at between 30 and 40°C. The residue was dissolved in methanol (15L) and aqueous sodium hydroxide (2M, 4.34L) added before heating at 65-67°C for 4h. The mixture was cooled and the solvents removed under vacuum at between 35 and 40°C until water started to distil. The residue was diluted with water (15L). The solid phosphine oxide was filtered off, washed with water (2.5L) and the filtrate separated. The aqueous phase was washed with methyl t-butyl ether (5L and 3.5L), before acidification with hydrochloric acid solution (5M, 1.9L) in the presence of methyl t-butyl ether (10L). The organic phase was separated and the aqueous phase reextracted with methyl t-butyl ether (5L). The combined organic extracts were washed with saturated brine (2 x 1L) and the solvent removed under vacuum. Methanol (2L) was added and then removed under vacuum, this step was then repeated. The residue was brought to a total weight of 4.0kg by addition of methanol and stirred at ambient temperature to crystallise the product. Filtration of the solid and washing with chilled (ca 0°C) methanol (500mL) gave, after vacuum drying at 40°C, the title compound (654g, 41% yield after correction for residual solvent). NMR was consistent with the above structure.

Preparation 8: (2*R*)-2-(4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid

(*E*)-2-(4-Cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid (Preparation 7, 110g, 0.327mol) was dissolved in MeOH/Toluene 5:1 (1.4L). In a 40mL

Schlenk flask was placed [Rh(nbd)$_2$](BF$_4$) (30.5mg, 0.08mmol) and All-MOD-Mandyphos (90.4mg, 0.08mmol), dissolved in MeOH (10mL) and stirred for 1h at RT. This catalyst solution was then added to the (*E*)-2-(4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid solution and transferred to a 2.5L autoclave. The autoclave was pressurized to 50 bar and heated to 30°C. After 18h the pressure was released and the solution transferred to a 3L flask. Active charcoal (3g) was added to the reaction mixture, stirred for 1h and the charcoal removed by filtration. The solution was further filtered over Hyflo and a Zeta-Bond filter. The solution thus obtained was concentrated under partial pressure and the solid obtained further dried under high vacuum to give a solid (105g). The solid was placed in a 1.5L flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. Isobutylacetate (540mL) was added at RT and the suspension heated at 110°C until a clear solution was observed. Heptane (60mL) was added slowly at 110°C, the oil bath was then removed and the solution allowed to cool slowly. The reaction was stirred for a further 16h, the title compound filtered off and dried under high vacuum (77.2g, 70% yield, 99% ee). ^{1}H NMR (CDCl$_3$, 300.13 MHz) δ: 7.85 (2H, Aryl H, d, J_{HH} = 6.6 Hz), 7.50 (2H, Aryl H, d, J_{HH} = 6.6 Hz), 3.95 (br d, 2H), 3.80 (t, 1H, C*H*CH$_2$, J_{HH} = 7.8 Hz), 3.35 (m, 2H), 2.45 (m, 1H), 2.10 (m, 1H), 1.75 (m, 1H), 1.60 (m, 2H), 1.50-1.20 (m, 5H), 1.05 (m, 2H).

Example 1

a) 2-(Tert-butoxycarbonylamino)-5-fluorothiazole

2-(Tert-butoxycarbonylamino)thiazole (10g, 0.050mol) in THF (0.2L) was cooled to -50°C under argon. tBuLi solution in pentane (60mL of a 1.7M solution, 0.102mol, 2.05eq) was added over a period of 30min and the temperature kept below -40°C. The suspension thus obtained was stirred at -50°C for 30min. A solution of N-fluorobenzenesulfonimide (NFSi) was prepared (22.0g, 0.07mol in 70mL THF, 1.4eq) and 50mL of this solution (1eq) was added over a 5min period and the temperature kept under -40°C. The reaction was stirred for 20min at -50°C. Then tBuLi (10mL, 0.017mol, 0.35eq) and the NFSi solution (10mL, 0.4eq) added. The solution thus obtained was stirred at -50°C for 45min and then added to saturated NH$_4$Cl solution (300mL). The organic phase was separated and the aqueous phase further washed with diethylether (100mL). The combined organic fractions were washed with brine (20mL) solution and dried (Na$_2$SO$_4$). The solvent was removed and the solid further dried to afford a brown solid. To this crude product was added trifluoroethanol (60mL) and formic acid (0.6mL). The suspension was heated to 85°C until it gave a solution. The flask was then cooled to RT and the precipitate thus formed filtered off to afford, after drying under high vacuum, the title compound (6.4g, contains 2.3% of starting material according to HPLC at

275nm). After a second crystallisation (trifluoroethanol (22mL) and formic acid (0.22mL) for 20min at 85°C), the title compound was obtained as an off white solid (4.6g, contains 1% of starting material, 97.5% pure by HPLC). ^{1}H NMR ($CDCl_3$) δ: 6.90 (1H, d, C<u>H</u>CF), 1.60 (9H, s, Boc-H).

b) 5-Fluorothiazol-2-ylamine hydrochloride

2-(Tert-butoxycarbonylamino)-5-fluorothiazole (4.6g, 21.1mmol) was dissolved in dioxane (25mL). HCl gas was bubbled through the solution for 4h, then diethyl ether (50mL) was added to give a suspension which was filtered off. The solid was dried in high vacuum to afford the title compound (3.03g, 19.7mmol, 93% yield). ^{1}H NMR (D_2O) δ: 7.00 (1H, d); *m/z* = 119.0 $[M + H]^+$.

Example 2: Preparation of 2-amino-5-fluorothiazole

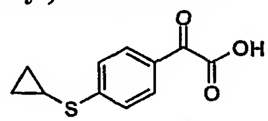
5-Fluorothiazol-2-ylamino hydrochloride (5.50g) was partitioned between Et_2O (100mL) and saturated aqueous $NaHCO_3$ (100mL). The aqueous phase was further extracted with Et_2O (100mL), then the combined organic extracts were washed with brine (50mL), before being dried ($MgSO_4$). Filtration and solvent evaporation furnished the free base (3.83g).

Example 3: Preparation of (2*R*)-2-(4-cyclopropanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide

A mixture of CH_2Cl_2 (1.35L) and DMF (35.9mL, 0.465mol, 1.5eq) was cooled to -20°C and oxalylchloride (39.4mL, 0.465mol, 1.5eq) was added slowly. After stirring for 45min (2*R*)-2-(4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (Preparation 8, 105.0g, 0.310mol, 1eq) was added. The reaction was stirred at -20°C for 1h. Collidine (185mL, 1.395mol, 4.5eq) was then slowly added and the reaction mixture was stirred for 15min before the addition of 5-fluorothiazol-2-ylamine hydrochloride (Example 1b, 52.7g, 0.341mol, 1.1eq) was at -15°C. The resulting suspension was kept at -15°C for 2h after which the ice bath was removed and the reaction slowly warmed up to RT over a period of 2h. The mixture was evaporated to dryness to afford a semi-solid to which was added portionwise 4N HCl solution (1.5mL). The product was extracted with ethylacetate (3L) and the organic fraction further washed with water (1L) and saturated $NaHCO_3$ solution (1L). The solvent was removed under partial vacuum to give the title compound (135g). Characterising data was consistent with the formation of the title compound.

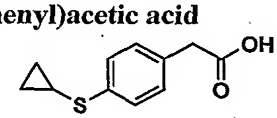
Example 4: Preparation of 2(*R*)-2-(4-cyclopropanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-((*R*)-3-oxocyclopentyl)propionamide

a: (4-Cyclopropylsulfanylphenyl)oxoacetic acid



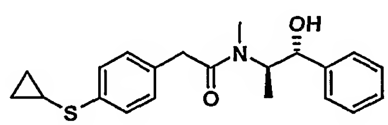
2M aqueous NaOH (163mL) was added to a solution of ethyl (4-cyclopropylsulfanylphenyl)oxoacetate (40.62g, 162.5mmol) in EtOH (200mL) and the stirred mixture heated at 60°C for 2h. After cooling, the mixture was concentrated to 150mL and washed with ether (2x100mL). Sufficient concentrated HCl was then added to adjust the pH to 1 and the resulting precipitate was extracted into EtOAc (2x300mL). The combined organic phases were washed with water (3x100mL), brine (200mL) and dried ($MgSO_4$). Removal of the solvent gave the title compound: *m/z* (ES^-) = 221.0 $[M-H^+]^-$.

b: (4-Cyclopropylsulfanylphenyl)acetic acid



Hydrazine hydrate (14.19g, 283.5mmol) was cooled to -50°C and (4-cyclopropylsulfanylphenyl)oxoacetic acid (12.6g, 56.7mmol) added in one portion. The vigorously-stirred slurry was warmed firstly to rt and then at 80°C for 5min. Solid KOH (8.76g, 156.5mmol) was added in four equal portions and the resulting solution heated at 100°C for 20h. On cooling to rt, water (25mL) was added and the aqueous phase washed with Et_2O (20mL). The ethereal phase was itself washed with water (2x15mL) and sufficient concentrated HCl added to the combined aqueous phases to adjust the pH to 1. The resulting precipitate was then extracted into EtOAc (2x300mL) and the combined organic phases washed with water (3x100mL), brine (200mL) then dried ($MgSO_4$). Evaporation of the solvent gave the title compound: *m/z* (ES^-) = 207.1 $[M-H^+]^-$.

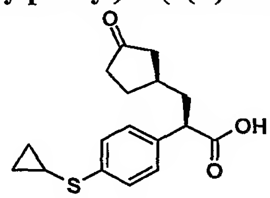
c: 2-(4-Cyclopropylsulfanylphenyl)-*N*-(2(*R*)-hydroxy-1(*R*)-methyl-2-phenylethyl)-*N*-methylacetamide



Anhydrous acetone (148mL) was added to (4-cyclopropylsulfanylphenyl)-acetic acid (16.41g, 78.8mmol) and K_2CO_3 (32.67g, 236.4mmol) to form a slurry which was cooled to -10°C with stirring. Neat trimethylacetyl chloride (10.2mL, 82.74mmol) was introduced dropwise, ensuring the temperature did not exceed -10°C during the addition. The reaction

mixure was stirred at -10°C for 20min, warmed to 0°C for 20min then cooled to –15°C and solid (1(*R*),2(*R*))-(-)-pseudoephedrine (19.53g, 118.2mmol) was added in one portion. After 10min, the reaction mixture was brought to rt, where stirring was continued for 1.5h. Water (100mL) was added and the mixture extracted with EtOAc (500mL). The organic phase was washed with water (2x100mL) and the combined aqueous layers back-extracted with EtOAc (2x250mL). The combined organic layers were then washed with brine (100mL) and dried ($MgSO_4$). The solvent was removed and the solid yellow residue recrystallized from EtOAc-IH to give the title compound: *m/z* (ES^+) = 356.1 $[M+H]^+$.

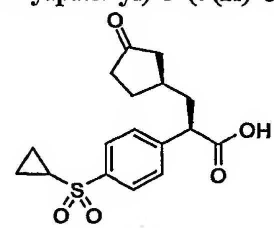
d: 2(*R*)-(4-Cyclopropylsulfanylphenyl)-3-(3(*R*)-oxocyclopentyl)propionic acid



LHMDS (162mL of a 1M solution in THF, 162mmol) was diluted with anhydrous THF (161mL) and cooled to -20°C with stirring. A solution of 2-(4-cyclopropylsulfanylphenyl)-*N*-(2(*R*)-hydroxy-1(*R*)-methyl-2-phenylethyl)-*N*-methylacetamide (30g, 84.4mmol) in anhydrous THF (245mL) was added *via cannula* over 10min, ensuring the reaction temperature remained below -15°C throughout the addition. The reaction was allowed to warm to -7°C over 30min then cooled to -12°C and a solution of 7(*S*)-iodomethyl-2(*S*),3(*S*)-diphenyl-1,4-dioxaspiro[4,4]nonane (27g, 64.2mmol) in a mixture of anhydrous THF (111mL) and DMPU (18.9mL) added *via cannula* over 10min, ensuring the reaction temperature remained below -7°C throughout. The reaction was warmed to 2°C and stirred for 4.5h before being poured into a mixture of toluene (770mL) and 20% aqueous NH_4Cl (550mL). After stirring vigorously, the organic layer was separated and washed with 20% aqueous NH_4Cl (550mL) and brine (100mL). The aqueous phases were combined and extracted with EtOAc (500mL) which, after separation, was washed with brine (100mL). The combined organic phases were dried ($MgSO_4$), filtered, evaporated and the resulting oil purified by flash chromatography (IH-EtOAc, 9:1 changing incrementally to 1:1) to give 2(*R*)-(4-cyclopropylsulfanylphenyl)-3-(2(*S*),3(*S*)-diphenyl-1,4-dioxaspiro[4.4]non-7(*R*)-yl)-*N*-(2(*R*)-hydroxy-1(*R*)-methyl-2-phenylethyl)-*N*-methylpropionamide: *m/z* (ES^+) = 648.3 $[M+H]^+$. A stirred solution of this amide (30.7g, 47.38mmol) in 1,4-dioxane (62mL) was diluted with 4.5M aqueous H_2SO_4 (61.5mL) and the resulting mixture heated under gentle reflux for 18h. After cooling on ice, water (162mL) was added and the mixture extracted with EtOAc (250mL). The aqueous layer was separated and extracted further with EtOAc (2x150mL) and

the combined organic phases washed with water (3x200mL), ensuring the final wash was pH neutral, and brine (100mL). After drying ($MgSO_4$) and filtering, the solvent was removed and the residue purified by flash chromatography (CH_2Cl_2 then CH_2Cl_2-THF, 5:1 changing to 3:1) to give the title compound: m/z (ES^+) = 305.1 $[M+H]^+$.

e: 2(*R*)-(4-Cyclopropanesulfonylphenyl)-3-(3(*R*)-oxocyclopentyl)propionic acid



A stirred solution of 2(*R*)-(4-cyclopropylsulfanylphenyl)-3-(3(*S*)-oxocyclopentyl)propionic acid (5.0g, 16.43mmol) in CH_2Cl_2 (250mL) was cooled to 1°C on ice and 70% *m*CPBA (8.099g, 32.85mmol) added portionwise, maintaining the temperature below 3°C. After 6h the solvent was removed and the residue purified by flash chromatography (1%AcOH in CH_2Cl_2 then THF) to give the title compound: m/z (ES^+) = 337.1 $[M+H]^+$.

f: 2(*R*)-2-(4-Cyclopropanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-((*R*)-3-oxocyclopentyl)propionamide

A solution of 2(*R*)-(4-cyclopropanesulfonylphenyl)-3-(3(*R*)-oxocyclopentyl)propionic acid (893mg, 2.65mmol) in anhydrous CH_2Cl_2 (38mL) was cooled to 0°C and a solution of oxalyl chloride (0.408g, 3.21mmol) in anhydrous CH_2Cl_2 (2mL) added dropwise, maintaining the temperature at 0°C during the addition. Dry DMF (0.08mL) was added and the reaction mixture stirred 2.5h. A solution of 2-amino-5-fluorothiazole free base (Example 2, 345mg, 2.92mmol) in anhydrous CH_2Cl_2 (6mL) was introduced slowly, followed by pyridine (0.53mL, 5.31mmol) and the mixture stirred at 0°C for 2h then at rt overnight. The solution was diluted with CH_2Cl_2 (150mL) and washed with aqueous 5%w/v citric acid (2x30mL), saturated aqueous $NaHCO_3$ (2x30mL), water (50mL) and brine (50mL). The organic phase was dried ($MgSO_4$), evaporated and the residue purified by flash chromatography (IH-EtOAc, 3:2) to afford the title compound. Characterising data was consistent with the formation of the title compound.

Example 5

a) 2-Acetamido-5-fluorothiazole

2-Acetamidothiazole (215mg, 1.51mmol) was added to a stirred solution of Selectfluor® (714mg, 2.02mmol) in anhydrous MeCN (20mL). The mixture was heated under

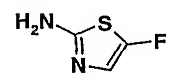
reflux for 16.5h, then the solvent was evaporated off under reduced pressure. The residue was partitioned between EtOAc (60mL) and H_2O (30mL). The aqueous phase was extracted further with EtOAc (30mL), then the combined organic extracts were washed with H_2O (30mL) and saturated aqueous $NaHCO_3$ (30mL), before being dried ($MgSO_4$). Filtration, solvent evaporation, and flash chromatography (Isohexane–EtOAc, 4:1 to 1:1) furnished the title compound as a white solid (117mg, 48%): RT = 2.40 min; m/z = 161.0 $[M+H]^+$.

b) 5-Fluorothiazol-2-ylamine hydrochloride

A stirred mixture of 2-acetamido-5-fluorothiazole (6.3g, 39.4mmol) and 2M HCl (150mL) was warmed at 70–75°C for 16 h. The reaction was evaporated to dryness, then PhMe was added, before being evaporated off to remove any residual water. The remainder was stirred with THF (50mL), before being collected and dried to furnish the title compound: δ_H (D_2O): 7.00 (1H, d), m/z = 119.0 $[M+H]^+$.

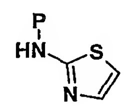
WHAT IS CLAIMED IS:

1. A process for the production of a compound of formula (I):



(I)

or an acid addition salt thereof, comprising fluorination of a compound of formula (II):



(II)

wherein P is a protecting group followed by removal of the protecting group and optional salt formation.

2. The process according to claim 1 wherein the protecting group is acetyl, pivaloyl, or tert-butoxycarbonyl (Boc).

3. The process according to claim 1 or 2 wherein the protecting group is tert-butoxycarbonyl (Boc).

4. The process according to any one of the preceding claims wherein the fluorination reagent is an electrophilic fluorinating agent.

5. The process according to claim 4 wherein the fluorination reagent comprises an active N-fluorine bond.

6. The process according to claim 5 wherein the fluorination reagent is a N-fluorosulfonmide.

7. The process according to claim 6 wherein the fluorination reagent is N-fluorobenzenesulfonimide.

8. The process according to any one of the preceding claims wherein the compound of formula (II) is deprotonated using an organolithium reagent.

9. The process according to claim 8 wherein the compound of formula (II) is deprotonated using about 2 equivalents of tert-butyl lithium.

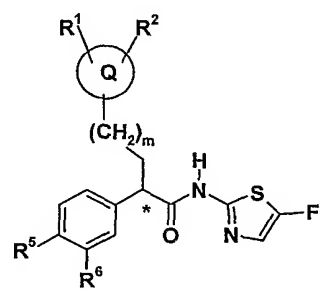
10. The process according to any one of the preceding claims which is conducted in a polar aprotic solvent.

11. The process according to claim 8 wherein the solvent is tetrahydrofuran.

12. The process according to any one of claims 1 to 3 wherein the fluorination reagent is 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

13. The process according to any one of the preceding claims wherein the salt of the compound of formula (I) is the hydrochloride salt.

14. A process for the production of a compound of formula (III), or a pharmaceutically acceptable salt thereof:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

Q is an aryl, a 5- or 6-membered heteroaryl, or a 4–8-membered heterocyclic ring;

R^1 and R^2 each independently are hydrogen, hydroxy, halogen, cyano, nitro, vinyl, ethynyl, methoxy, OCF_nH_{3-n}, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, CHO, or $C_{1-2}alkyl$ optionally substituted with 1-5 independent halogen, hydroxy, cyano, methoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, or SO_2CH_3 substituents; or R^1 and R^2 together form a carbocyclic or heterocyclic ring; or R^1 and R^2 may be taken together to represent an oxygen atom attached to the ring via a double bond;

R^5 and R^6 each independently are hydrogen, hydroxy, halogen, cyano, nitro, CO_2R^7, CHO, COR^8, $C(OH)R^7R^8$, $C(=NOR^7)R^8$, $CONR^9R^{10}$, SR^7, SOR^8, SO_2R^8, $SO_2NR^9R^{10}$,

$CH_2NR^9R^{10}$, NR^9R^{10}, $N(C_{0-4}alkyl)SO_2R^8$, $NHCOR^7$, or C_{1-4}alkyl group, C_{2-4}alkenyl group, C_{2-4}alkynyl group, C_{1-4}alkoxy group, aryl group, or heteroaryl group, wherein any group optionally is substituted with 1-6 independent halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, CF_nH_{3-n}, aryl, heteroaryl, $-COC_{1-2}$alkyl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, SCH_3, $SOCH_3$, SO_2CH_3, or $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$ substituents; or R^5 and R^6 together form a 5–8-membered carbocyclic or heterocyclic ring;

R^7 is hydrogen, or C_{1-4}alkyl group, C_{2-4}alkenyl group, C_{2-4}alkynyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4–7-membered heterocyclic group, wherein any group optionally is substituted with 1-6 independent halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, C_{3-7}cycloalkyl, 4–7-membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, CO_2H, $-COC_{1-2}$alkyl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, or $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$ substituents;

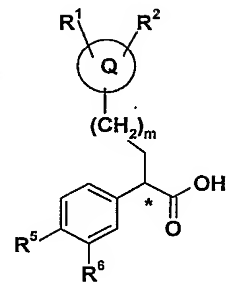
R^8 is C_{1-4}alkyl group, C_{2-4}alkenyl group, C_{2-4}alkynyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4–7-membered heterocyclic group, wherein any group optionally is substituted with 1-6 independent halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, C_{3-7}cycloalkyl, 4–7-membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, CO_2H, COC_{1-2}alkyl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, or $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$ substituents;

R^9 and R^{10} each independently are hydrogen, or C_{1-4}alkyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4–7-membered heterocyclic group, wherein any group optionally is substituted with 1-6 independent halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, C_{3-7}cycloalkyl, 4–7-membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, COC_{1-2}alkyl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, or $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$ substituents; or R^9 and R^{10} together form a 6–8-membered heterobicyclic ring system or a 4–8-membered heterocyclic ring which optionally is substituted with 1–2 independent C_{1-2}alkyl, CH_2OCH_3, COC_{0-2}alkyl, hydroxy, or SO_2CH_3 substituents;

n is 1, 2 or 3; and

m is 0 or 1;

which comprises the condensation of a compound of formula (I) produced according to any one of the preceding claims or a salt thereof, with a carboxylic acid of formula (IV) or an activated derivative thereof:



(IV)

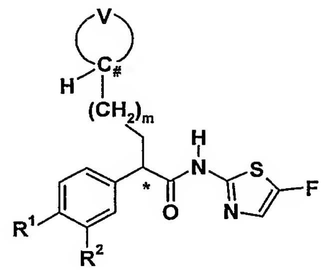
wherein R^1, R^2, R^5, R^6, Q and m are as defined above.

15. The process according to claim 14 wherein in the compounds of formula (III) the carbon atom linking the aryl ring and Q-bearing sidechain to the carbonyl carbon is in the (*R*)-configuration.

16. The process according to claim 14 or 15 wherein in the compounds of formula (III):
Q is 4-tetrahydropyranyl;
R^1 and R^2 are hydrogen;
R^5 is SO_2R^8, or $SO_2NR^9R^{10}$;
R^6 is hydrogen;
R^8 is a C_{3-5}cycloalkyl group or a 4–6-membered heterocyclic group, and, in addition;
R^9 and R^{10} are independently C_{0-4}alkyl, provided that R^9 and R^{10} are not both hydrogen; and
m is 0.

17. The process according to any one of claims 14 to 16 wherein in the compounds of formula (III) R^5 is SO_2cyclopropyl.

18. A process for the production of a compound of formula (VII), or a pharmaceutically acceptable salt thereof:



(VII)

wherein V is $(CH_2)_k$ where one CH_2 group may optionally be replaced by CH(OH), C=O, C=NOH, $C=NOCH_3$, CHX, CXX^1, $CH(OCH_3)$, $CH(OCOCH_3)$, $CH(C_{1-4}alkyl)$, or $C(OH)(C_{1-4}alkyl)$;

X and X^1 are independently selected from fluoro and chloro;

R^1 and R^2 are independently selected from hydrogen, halogen, hydroxy, amino, cyano, nitro, SR^3, SOR^3, SO_2R^3, $SO_2NR^4R^5$, $NHSO_2R^3$, or a C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, or heteroaryl group, wherein any group is optionally substituted with 1 to 5 substituents independently selected from halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, CF_nH_{3-n}, aryl, heteroaryl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, SCH_3, $SOCH_3$, SO_2CH_3, and $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$;

R^3 is a C_{1-4}alkyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4- to 7-membered heterocyclic group, wherein any group is optionally substituted with 1 to 5 substituents independently selected from halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, C_{3-7}cycloalkyl, 4- to 7-membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, COC_{1-2}alkyl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, and $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$;

R^4 and R^5 are independently hydrogen, or a C_{1-4}alkyl group, C_{3-7}cycloalkyl group, aryl group, heteroaryl group, or 4- to 7-membered heterocyclic group, wherein any group is optionally substituted with 1 to 5 substituents independently selected from halogen, cyano, nitro, hydroxy, C_{1-2}alkoxy, $-N(C_{0-2}alkyl)(C_{0-2}alkyl)$, C_{1-2}alkyl, C_{3-7}cycloalkyl, 4- to 7-membered heterocyclic ring, CF_nH_{3-n}, aryl, heteroaryl, $-CON(C_{0-2}alkyl)(C_{0-2}alkyl)$, $SOCH_3$, SO_2CH_3, and $-SO_2N(C_{0-2}alkyl)(C_{0-2}alkyl)$;

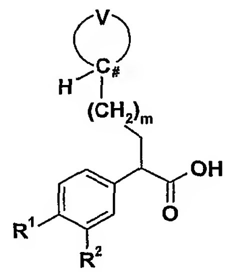
or R^4 and R^5 together form a 4- to 8-membered heterocyclic ring which is optionally substituted with 1 or 2 substituents independently selected from C_{1-2}alkyl and hydroxy;

k is an integer from 2 to 7;

m is 0 or 1; and

n is 1, 2 or 3.

which comprises the condensation of a compound of formula (I) produced according to any one of claims 1 to 10 or a salt thereof, with a carboxylic acid of formula (VIII) or an activated derivative thereof:



(VIII)

wherein V, R^1, R^2 and m are as defined for formula (VII).

19. The process according to claim 18 wherein in the compounds of formula (VII) the group formed by –HC< and >V represents oxocycloalkyl or hydroxycycloalkyl.

20. The process according to claim 18 or 19 wherein in the compounds of formula (VII) R^1 and R^2 are not both hydrogen.

21. The process according to claim 20 wherein in the compounds of formula (VII) R^1 is SO_2C_{3-4}cycloalkyl.

22. The process according to any one of claims 18 to 21 wherein in the compounds of formula (VII) R^4 and R^5 are independently hydrogen or C_{1-4}alkyl.

23. The process according to any one of claims 18 to 22 wherein in the compounds of formula (VII) m is 0.

24. The process according to any one of claims 18 to 23 wherein in the compounds of formula (VII) k is 4 or 5.

25. A pharmaceutical composition comprising a compound of formula (III) or (VII), or a pharmaceutically acceptable salt thereof, produced according to the method of any one of claims 14 to 24, in combination with a pharmaceutically acceptable diluent or carrier.

26. A method for the prophylactic or therapeutic treatment of a condition where activation of glucokinase is desirable comprising a step of administering an effective amount of a compound of formula (III) or (VII), produced according to the method of any one of claims 14 to 24, or a pharmaceutically acceptable salt thereof.

27. A method for the prophylactic or therapeutic treatment of hyperglycemia or diabetes comprising a step of administering an effective amount of a compound of formula (III) or (VII), produced according to the method of any one of claims 14 to 24, or a pharmaceutically acceptable salt thereof.

28. A method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering an effective prophylactic amount of a compound of formula (III) or (VII), produced according to the method of any one of claims 14 to 24, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/003170

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/40 C07D277/46 C07D417/12 A61K31/426 A61K31/427
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/063179 A (ELI LILLY AND COMPANY) 29 July 2004 (2004-07-29) cited in the application the whole document, particularly examples 38 and 65	1-28
Y	KOBARFARD F ET AL: "Attempted syntheses of aminofluorothiophenes" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 36, no. 5, 1999, pages 1247-1251, XP002350219 the whole document	1-28
P,X	WO 2004/072031 A (OSI PHARMACEUTICALS, INC.) 26 August 2004 (2004-08-26) cited in the application the whole document, particularly examples 10,11,94,96,107,115-117 and 120	14-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2005	16/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

International Application No
PCT/GB2005/003170

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/072066 A (OSI PHARMACEUTICALS, INC.) 26 August 2004 (2004-08-26) the whole document, particularly examples 43,53,54,60 and 63	14-28
Y	WO 03/095438 A (F. HOFFMANN-LA ROCHE AG) 20 November 2003 (2003-11-20) the whole document	14-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/003170

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB2005/003170

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 2004063179	A	29-07-2004	AU	2003297291	A1	10-08-2004
			CA	2509086	A1	29-07-2004
			EP	1585739	A1	19-10-2005
WO 2004072031	A	26-08-2004	AU	2004212500	A1	26-08-2004
WO 2004072066	A	26-08-2004	NONE			
WO 03095438	A	20-11-2003	AU	2003232204	A1	11-11-2003
			BR	0309546	A	15-02-2005
			CA	2482346	A1	20-11-2003
			CN	1649859	A	03-08-2005
			EP	1501815	A1	02-02-2005
			HR	20040953	A2	30-06-2005
			MA	27113	A1	20-12-2004

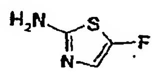
INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/003170

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

A process for the production of fluorinated compound (I) comprising fluorination of a protected aminothiazole.

Compounds (I) are useful in the preparation of activators of glucokinase.



(I)